REMARKS

Claims 1-4, 11, 12, 16, and 21 have been examined on their merits. Although claims 1-26 were pending at the time of examination, claims 5-10, 13-15, 17-20, and 22-26 were withdrawn from consideration before examination.

With entry of this amendment, claims 1-28 will be pending; claims 5-10, 13-15, 17-20, and 22-26 remain withdrawn; claims 1-5, 9, 11, and 21 will be amended; claims 27 and 28 will be added.

Support for the amendments to claim 1 can be found in Examples 2 and 3 starting on page 40, line 22 and Figures 4-6 of the application as filed. Support for "approximately" can be found on page 23, lines 6-11 of the application as filed. Support for "at least approximately 30%" can be found in Figure 4B (compare the percentage of specific lysis in the presence of E7-E6 wt and E7-E6 PentM at an effector to target ration of 50:1) and in associated Example 2 of the application as filed. Support for how to measure immunogenicity can be found in Example 2 on page 41, lines 6-22 of the application as filed, discussing the Europium release assay, and in Example 3 on page 42, lines 14-27 of the application as filed, discussing tumor growth assays.

Support for "mutant" can be found throughout the specification and, *e.g.*, on page 16, lines 1-2 of the specification as filed.

Support for new claim 27 can be found in Example 3 starting on page 42, line 10 and in Figures 5 and 6 (compare, *e.g.*, the percentage of tumor free mice in the presence of E7-E6 and E7-E6 PentM of Figure 5A) of the specification as filed. Support for new claim 28 can be found on, *e.g.*, page 3, lines 21-22 of the specification as filed.

The remaining amendments are intended to clarify the subject matter of the claims. No new matter has been added by way of these amendments.

Applicants' Invention

The claimed invention is based on at least two discoveries. An E7 mutant fused to a mutated or unmutated E6 retains its immunogenicity while not inducing the degradation of Rb. An E6 mutant fused to a mutated E7 retains its immunogenicity while not inducing the degradation of p53.

As described on page 7, lines 9-14 and page 8, lines 28-31 of the specification as filed, most of the specific E6 and E7 point mutations disclosed in the instant application have been previously disclosed. However, one of ordinary skill in the art could not have predicted with a reasonable expectation of success whether the claimed combinations of certain mutations (*e.g.*, a mutated E7 fused to an unmutated E6) would remain immunogenic while not degrading, *e.g.*, Rb. The retained immunogenicity coupled with the absence of degradation is unexpected because one skilled in the art could not know in advance whether the claimed fused polypeptides would have folding difficulties, aggregation problems, rapid degradation, new properties, restored properties, or a combination thereof that would result in the loss of immunogenicity and/or the restoration of a wild-type ability to degrade.

Mutants lacking the ability to degrade Rb or p53 are desirable because these mutants are unlikely to transform or immortalize cells, unlike their wild-type counterparts. These mutants still maintain the ability to induce immunogenicity which can contribute to the prevention of cancer caused by human papillomavirus (HPV) infections.

In sum, the claimed mutant fusions are unexpectedly both safe (*i.e.*, lacking the ability to degrade Rb or p53) and effective (*i.e.*, maintaining their ability to induce immunogenicity). In contrast, wild-type fusions of E7 and E6, while retaining their immunogenicity, may not be safe because they retain their ability to degrade Rb and p53.

Furthermore, Applicants have discovered mutant fusions that unexpectedly are at least as immunogenic as wild-type fusion proteins. These mutant fusions are set forth in new claim 27.

Claim Rejection - 35 U.S.C. §103

The Examiner has rejected all of the examined claims as obviousness over Dalal *et al.* (Journal of Virology 1996, 70:683-688; "Dalal") in light of Bruck *et al.* (PCT Publication No. WO 99/10375, "Bruck"). According to the Examiner, Dalal discloses a series of E6 mutants mutated at amino acids 106 and 63 and teaches that these mutations neither affect the binding to nor the degradation of p53. The Examiner concedes that Dalal does not disclose fusions of E6 and E7. According to the Examiner, Bruck teaches a fusion of E6 and E7, describes that E7 can be mutated at amino acids 24 and 26, and discloses adjuvant and immunogenic compositions. The Examiner concludes that a person skilled in the art would be motivated to combine the E6 mutations of Dalal, the E6/E7 fusions of Bruck, and the E7 mutation of Bruck to form the claimed invention to induce immunogenicity in a host. Finally, the Examiner asserts that there would be no unexpected results in doing so.

To address this rejection, claim 1 has been amended by adding that "the mutant polypeptide retains at least approximately 30% of the immunogenicity of an isolated polypeptide comprising human wild-type papillomavirus E6 and E7 ." The amended claims are not obvious over Dalal in light of Bruck because, as discussed above, one of ordinary skill in the art would not reasonably expect that the claimed mutant fusion polypeptides would have at least approximately 30% of the immunogenicity of a fusion polypeptide that contains wild-type E6 and E7 while containing mutations that prevent the degradation of Rb and p53.

The teachings of Dalal and Bruck do not provide a reasonable expectation that the claimed mutants would be immunogenic and lack the ability to degrade Rb and p53. Dalal merely describes E6 mutants that lack the ability to degrade p53 and to immortalize cells. Dalal does not teach or suggest that E6 mutants retain their immunogenicity and certainly does not provide a reasonable expectation that an E6 mutant in a fusion with an E7 mutant retains its immunogenicity while lacking the ability to degrade p53.

Bruck discloses wild-type E6E7 fusions, E7 mutants without transforming capacity resulting from the reduced ability to bind Rb, and E7 mutants fused to an immunologically active protein (*e.g.*, protein D). Bruck demonstrates that protein D-E7 fusions induce immunogenicity. However, Bruck does not provide a reasonable expectation that fusions containing an E7 mutant and a mutated or unmutated E6 would retain immunogenicity while lacking the ability to degrade Rb.

Conclusion

In view of the above amendments and remarks, Applicant submits that this application is in condition for favorable reconsideration. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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